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Biomedical issues in transgender health research

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Summary. Transgender is an umbrella term that refers to those individuals whose gender identity (i.e. the person's internal sense of gender) differs from the sex assigned at birth. Although the main international institutions (e.g. World Health Organization) have included, among the priority objectives in the fight against inequalities in health, actions aimed at protecting transgender people, exposure to violence, stigma and discrimination is still high for this population, which favors the risk of inadequate healthcare. To date we do not know exactly how many transgender people there are, what their health status is or what health services they need, which poses a problem for health planning. Indeed, transgender people share many of the needs of the general population, but may have special needs, such as those related to gender-affirming hormone and/or surgical treatments. The purpose of this review is to provide an overview of the main health issues of the transgender population with particular attention to the Italian scenario.

Key words. Transgender, transsexual, health disparity, gender affirming hormone treatment, gender affirming surgery.

Questioni biomediche nella ricerca sulla salute transgender

Riassunto. Il termine transgender è un termine ombrello usato per descrivere persone con una vasta gamma di identità di genere che sono diverse dal sesso assegnato alla nascita. Sebbene le principali istituzioni internazionali (per esempio, l'Organizzazione Mondiale della Sanità) abbiano da tempo inserito tra gli obiettivi prioritari nella lotta contro le disuguaglianze nell'assistenza sanitaria azioni efficaci a tutela della salute delle persone transgender, questa fascia di popolazione è oggetto di discriminazione e presenta significativi ostacoli nell'accesso ai servizi sanitari e nell'utilizzo delle cure. Le persone transgender condividono molte delle esigenze sanitarie della popolazione generale, ma possono avere peculiari necessità specialistiche come quelle correlate al trattamento ormonale e alla chirurgia di affermazione di genere. La scarsità di dati disponibili relativamente alla numerosità e allo stato di salute generale di questa fascia di popolazione ostacola tuttavia un'efficace e mirata programmazione sanitaria. Lo scopo di questa *review* è quello di fornire una panoramica delle principali problematiche sanitarie relative alla popolazione transgender con una particolare attenzione al contesto italiano.

Parole chiave. Transgender, transessuale, disuguaglianze di salute, trattamento ormonale di affermazione di genere, trattamento chirurgico di affermazione di genere.

Introduction

The main international institutions (e.g. World Health Organization, WHO) have included among the priority objectives in the fight against inequalities in healthcare, in a perspective centered on the different needs of the population, that of promoting actions aimed at protecting transgender people[1,2]. However, to date, exposure to violence, stigma and discrimination is still high for this population, which favors the risk of inadequate healthcare[3,4].

Transgender is an umbrella term that refers to those persons whose gender identity (i.e. the person's internal sense of gender) differs from the sex that was assigned at birth. It can be abbreviated to 'trans'. A transgender man is someone with a male gender identity and a female birth-assigned sex; a transgender woman is someone with a female gender identity and a male birth-assigned sex. A non-transgender person can be referred to as cisgender ('cis' means same side in Latin). It is important to stress that the term 'transgender' does not refer to sexual orientation. Indeed, trans people can be heterosexual, bisexual, lesbian, homosexual, asexual, just like cisgender people. Some, but not all, transgender people choose to affirm their gender identity by socially transitioning (i.e., living as their experienced gender socially, at work or in an educational institution, with friends and family, outside the home) and some, in addition, choose to modify their body using gender-affirming hormone and/or surgical treatments.

Terminology evolves constantly and terms used in the past may become obsolete and can be perceived as pejorative. For example, the term 'transsexual' is mostly now limited to the legal and medical literature. In the International Classification of Diseases and Health Related Problems (ICD-10), 10th edition[5], the term 'transsexualism' is used as a diagnostic term to describe individuals whose sex assigned at birth does not match their gender identity and wish gender-affirming treatment. This term is included in the chapter 5, entitled "Mental and behavioral disorders", in a section called "Disorders of adult personality". It is well documented that mental disorders are highly-stigmatized conditions in most areas of the world[6], and the psychopathologization of

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gender incongruence confers a stigma that is particularly pernicious, thereby also supporting discriminatory behavior. Thus, with the aim of the de-psychopathologization of trans identities, in the forthcoming ICD-11 that was released in June 2018 as an advance preview (http://www.who.int/classifications/icd/en/), in the chapter Conditions related to sexual health, the diagnostic term for transsexualism has been reformulated as "gender incongruence in adolescents and adulthood", "gender incongruence in childhood", and "gender incongruence, unspecified".

Gender dysphoria (GD) refers to a profound distress or discomfort caused by the discrepancy between birth-assigned sex and gender identity[7]. The category of GD is included in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), and its inclusion in the DSM is strongly criticized because it continues to 'pathologize' transgender expressions and identities[8]. It should be noted that only some transgender people experience GD at some point in their lives and the decision regarding medical transition among transgender people may vary. For some people, social transition may be enough, without the need for further physical intervention. Other people access transgender health services in order to obtain gender-affirming treatments. In Italy, a diagnosis of GD by a mental health expert is demanded by most healthcare professionals as a requirement for access to gender-affirming interventions.

Finally, being transgender is not the same as being intersex, a term used to define individuals who are born with sex characteristics that do not fit typical binary notions of male or female bodies (chromosomal, hormonal, gonadal, or genital). However, intersex people may experience GD and consequently request gender-affirming treatments.

In this review key points on transgender health issue are addressed with a particular focus on the Italian scenario.

The size of the transgender population

The efforts made so far to obtain realistic estimates of transgender prevalence have encountered enormous difficulties. The main problem lies in understanding which criteria to use in the epidemiological analysis and, therefore, the subjects to be considered; indeed, the estimates are usually made on subgroups that are easier to identify, for example on people who turn to specialized centers requiring hormonal or surgical treatment, and not on the general population with gender incongruence, with a consequent underestimation of the data[9,10]. Taking into account these methodological limitations, the estimates to date suggest a worldwide prevalence of between 0.5 and 1.3% for birth-assigned males and between 0.4% and 1.2% for birth-assigned females[9,10]. A recent study by Ahs JW et al.[11], carried out on the general adult population of Stockholm County (Sweden), suggests a higher percentage than that reported above. "Feeling like someone of a different sex" was reported by 2.3% (95% CI: 2.1% ± 2.6%) and "wanting to live as or be treated as a person of another sex" was reported by 2.8% (95% CI, 2.4% ± 3.1%) of the general population[11]. In Italy, the only data available at the current time derive from an epidemiological study published in 2011 that included an adult transsexual population undergoing surgical treatment in the period between 1992 and 2008. In this study, the overall prevalence was estimated as 0.9 per 100,000 inhabitants, and 1.5 per 100,000 inhabitants in transsexual women and 0.4 per 100,000 inhabitants in transsexual men[12]. The numbers derived from this study, as from other international studies, represent a rough estimate of the data due to the absence of a standard assessment tool for the transgender population. However, it can be said that both in Italy and abroad the number of transgender people is constantly increasing, as testified to by the increase in associations and professionals in the medical areas (endocrinologists, surgeons, psychiatrists, psychologists, etc.) that deal with transgender health[13]. In any case, the existing data, although it underestimates the real data, should be considered a starting point and the National Health Service (NHS) would benefit from studies making it possible to define the actual size of this population for correct health planning.

Transgender population needs in terms of health

As regards healthcare, transgender people share many of the needs of the general population, but may have special needs, such as gender-affirming hormone treatment and gender-affirming surgical intervention[14,15]. In Italy, as in much of the world, access to healthcare services can be especially hard for transgender people due to a number of different factors (e.g. discrimination, structural barriers, lack of physician competence in transgender health). For this reason, they often rely on the services of medically unqualified people and/or engage in self-administered hormonal treatment[16].

To date, defining the general health status (average life span; perception of health status; prevalence and incidence of chronic oncological, cardiovascular, degenerative diseases, etc.) for this population, as well as the use of drugs, adverse reactions and the appropriateness of therapy is made very complex by the limited amount of scientific evidence on the matter[10]. An analysis of scientific literature data indicates that the most studied health indicators for transgender people are drug use, violence and victimization, as well as stigma and dis-

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crimination. Sexual and reproductive health and mental conditions (e.g. mood disorders, suicidal and non-suicidal self-injury, anxiety disorders) are the most frequently studied areas of transgender health[10]. In general, depressive symptoms, suicidality, interpersonal trauma exposure, anxiety, and general distress are consistently elevated amongst transgender adults[17]. It should be noted that transgender people are exposed to a variety of social stressors, including stigma, discrimination, and bias events that contribute to mental health problems[17].

Additionally, transgender people, particularly transgender women, carry a significantly higher burden of HIV infection and other sexually-transmitted infections than their cisgender counterparts[18,19]. However, transgender people continue to represent an underserved population both in clinical care and HIV prevention services[20]. One example of this is the lack of research on the interaction between antiretroviral treatments and the hormone regimens used in gender transition[21].

Many other crucial health areas remain undervalued, such as oncological, cardiovascular, and degenerative diseases[10]. This implies that there is no health surveillance activity in the transgender population.

Hormonal therapy and critical issues

Somatic interventions aim at aligning the body with the perceived gender; this medical approach includes gender-affirming hormone treatment and surgery[22-24]. Gender-affirming hormone treatment is prescribed by medical professionals although there is a black market, especially for oral contraceptives. In Italy, gender-affirming hormone treatment is refunded by NHS only in some regions, thereby creating inequalities at national level. In addition, the AIFA Resolution no. 1327 of 16/10/15 O.J. no. 259, 06/11/15 and subsequent amendment (AIFA Resolution no. 199 of 05/02/16 O.J. no. 45, 24/02/16), according to which testosterone can only be prescribed by endocrinologists, urologists and andrologists, generate inequality between transgender women, to whom estrogen can also be prescribed by a general practitioner, and transgender men, who are obliged to attend specialist visits.

The goal of gender-affirming hormone treatment is to reduce the secondary sex characteristics of the birth sex and to develop the desired ones. Currently, gender-affirming hormone treatment regimens are not standardized and comprise various forms, applications, and dosages of sex hormones. Briefly, in transgender women, it is necessary to decrease endogenous sex hormone levels (androgens) and to replace them with those of the desired gender, i.e., estrogens[22-24]. The administration of estrogens suppresses gonadotropin secretion and, consequently, androgen production. However, combined therapy with both estrogens and anti-androgens is more effective in reducing endogenous androgens to within the female range, thereby increasing the feminizing effects of estrogens. In Europe, the most commonly prescribed anti-androgen is oral cyproterone, which acts primarily as an androgen receptor blocker but also has some progesterone-like activity. Other potential options are the gonadotropin-releasing hormone (GnRH) agonists that inhibit gonadotropin secretion and, as a result, suppress testicular testosterone production[25]. GnRH analogues are increasingly prescribed, although their cost often precludes their use in transgender people.

In transgender men, gender-affirming hormone treatment consists in testosterone administration, following the general principle of hormone replacement treatment of male hypogonadism.

Pretreatment screening and regular medical monitoring are suggested during the endocrine transition and periodically thereafter[22-24]. In the following section, we summarize some of the possible adverse outcomes of gender-affirming hormone treatment. However, follow up data on the long-term effects and side effects of hormone treatment on health are still limited in the transgender population and no randomized controlled trials are available.

Gender-affirming hormone treatment, cardiovascular risk and metabolic disorders

Of the possible adverse outcomes of gender-affirming hormone treatment in the transgender population, cardiovascular disease is a specific area of concern. Available studies evaluating the impact of gender-affirming hormone treatment on cardiovascular disease show sparse and discordant results, because of the predominance of small and non-randomized trials[26,27]. The cardiovascular effects of gender-affirming hormone treatment in transgender persons can be monitored via several surrogate cardiovascular risk markers including changes to insulin sensitivity, lipid profiles, blood pressure, polycythemia and vein thrombosis. So far, there are no data on the impact of gender-affirming hormone treatment on cardiac function, including electrophysiological remodeling and the underlying molecular mechanisms. However, adaption or maladaptation to a new hormonal environment may predispose an individual to increased or under-estimated arrhythmogenic risk, especially in combination which channel-interfering drugs such as antidepressants. Therefore, given the paucity and poor quality of evidence due to the methodological limitations, heterogeneity of treatment, and exclusion of transgender people from large clinical trials on cardiovascular medications, further research is needed to better clarify the cardiovascular and metabolic effects of gender-affirming hormone treatment in both transwomen and transmen.

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However, some important differences in cardiovascular risk have been observed between these two subpopulations with respect to the general population.

Transgender women

According to a recent meta-analysis, including 3231 transgender women undergoing gender-affirming hormone treatment, with a follow-up range of between 3 months to 41 years, a significant increase in triglycerides was detected (at least amongst those treated with oral estrogen)[26]. Diabetes has been observed more frequently among transgender women than transgender men, but more research is required to better address this issue[28].

As regards the incidence of acute cardiovascular events, the largest available cohort study showed higher rates of venous thromboembolism and, to a lesser extent, ischemic stroke in transgender women compared to cisgender men and women, given the known prothrombotic actions of estrogen[29]. In addition, myocardial infarction rates were greater among transgender women than in matched cisgender women.

Transgender men

According to the above mentioned meta-analysis[26], which also included 1500 transgender men undergoing gender-affirming hormone treatment, an increase in total cholesterol and triglycerides levels, and a decrease in high-density lipoprotein cholesterol compared to the general population were observed. As far as acute cardiovascular events were concerned, the evidence was insufficient to draw conclusions regarding an increased risk for any of the acute cardiovascular events in transgender men[29].

Gender-affirming hormone treatment and cancer risk

Several malignant tumors, such as breast, ovary, endometrium, prostate, testicular and prostate cancer, are sex hormone-dependent[30]. Moreover, some benign brain tumors, in particular meningiomas and prolactinomas, occur more frequently in females than in males, raising the question as to the role of sex hormones in their pathogenesis[31]. As many transgender individuals receive, or self-treat, with lifelong cross-sex hormone treatment, sometimes at high doses, the carcinogenicity of hormonal therapy is an area of significant concern. Recently, systematic searches of medical literature have been conducted to identify cases of one or more presumably hormone-related malignancies (breast, ovary, endometrium, prostate, and testicular cancer) in transmen and transwomen and diagnosed after the initiation of cross-sex hormone treatment [33-37]. With regard to benign brain tumors, a retrospective chart study was conducted to assess their incidence in a cohort of transgender individuals attending the VU University Medical Centre in the Netherlands and receiving cross-sex hormone treatment[31]. The findings of these articles are presented below[31,33-37].

Transmen

Stone JP et al.[35] identified 17 individuals with breast cancer, of whom eight had taken gender-affirming hormones for 1-15 years, and 6 had also undergone a mastectomy. Transmen showed a younger median age at diagnosis (44.5 years) than natal females (62 years). Joint R et al.[34] identified ovarian cancer in 5 individuals, three of whom had taken gender-affirming hormones for 1–18 years. Braun H et al.[37] reported one case of endometrial cancer in a transman receiving testosterone therapy. The cancer was diagnosed 7 years after the initiation of hormonal treatment. In their retrospective chart study, Nota NM et al.[31] identified 3 cases of benign brain tumors: one prolactinoma and two somatotrophinomas. The single case of prolactinoma they observed was no different to the number expected using the incidence rates of a general Dutch female and male population. However, as somatotrophinomas are very rare, the two observed cases of somatotrophinomas were higher than expected.

Transwomen

Hartley RL et al.[36] identified 22 cases of breast cancer; seven cases had a positive family history for breast cancer, and one was BRCA2-positive (5 patients tested). Twenty of the 22 breast cancer cases were reported as having received estrogen therapy as part of their treatment and this information was not available for the remaining two cases. Transwomen were diagnosed at a younger age (median age 51.5 years) versus a natal male median age of 68 years and a natal female median age of 60 years. Ingham MD et al.[33] identified 10 cases of prostate cancer in transwomen who had been on hormone therapy for 6 to 41 years before diagnosis. The median age at diagnosis was of 63 years. Joint R et al.[34] identified one case of a transwoman diagnosed with a testicular germ cell carcinoma in situ who had been taking gender-affirming hormones for 2 years. Nota NM et al.[31], in their retrospective chart study, identified 20 cases of benign brain tumors: eight meningiomas, nine prolactinomas, two schwannomas and one adenoma. The incidence of meningiomas was higher in transwomen than in a general European female population and male population. Like meningiomas, prolactinomas occurred more frequently in transwomen compared to the general Dutch female and male population. At the time

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of diagnosis, most individuals (including those who have received orchiectomy) who were diagnosed with a meningioma or prolactinoma were still using cyproterone acetate.

According to the data available at the current time, the concerns regarding breast, ovary, endometrial, testicular, and prostate cancer in transgender populations, albeit biologically plausible, are neither adequately supported nor convincingly alleviated, due to a lack of well-designed epidemiologic studies[37]. For benign brain tumors alone, Nota NM et al.[31], based on the results of their study, hypothesized a hypothetically higher risk in transgender individuals receiving high-dose cross-sex hormone treatment. As for transgender individuals it is not possible to obtain high-level evidence of a positive or negative association between cross-sex hormone treatment and hormone-related tumors, future large well-designed longitudinal studies are needed to clarify the effect of cross-sex hormone treatment on hormone-dependent tumor development[37]. Moreover, as the main limitation of the existing data is the very small size of the available studies, multi-center studies are highly recommended in order to increase study power. Future studies should also control for the well-known risk factors associated with the hormone-dependent tumor of interest[34], such as, for example, family history of cancer for breast and ovarian cancer and obesity for breast cancer.

Until more conclusive evidence is available, screening for breast and reproductive organ tumors for both transgender males and females is highly recommended. It should be based on guidelines for the general population and the presence of organs in transgender individuals rather than gender identity or hormonal therapy status[22,37].

Gender-affirming hormone treatment and bone health

Sex steroid hormones are involved in bone growth and homeostasis. The role of sex hormones in the maintenance of bone mass during adulthood is demonstrated by the development of osteoporosis in both women and men after the interruption of sex steroid production[38,39]. Studies analyzing bone mineral density (BMD) in transgender women receiving gender-affirming hormone treatment have shown conflicting results. Indeed, some studies have shown that bone mass was preserved or significantly increased compared to baseline values, i.e. before initiation of feminizing hormone therapy[40-44]. On the other hand, some studies have shown a decrease in BMD in transwomen, suggesting that the androgen deprivation induced by anti-androgen administration could contribute to this finding[45,46]. The differences in results may be due to the regimens used and the duration of follow-up. In general, in transwomen known risk factors for osteoporosis include underutilization of hormones after gonadectomy or use of androgen blockers without or with insufficient estrogen.

In transgender men treated with testosterone either no change or an increase in BMD were detected compared to baseline values before initiating masculinizing hormone therapy[42,44,47-49]. Risk factors for osteoporosis in this population include oophorectomy before the age of 45 without optimal hormone replacement. On the whole, the quality of evidence was low and according to international guidelines clinicians should obtain BMD measurements when risk factors for osteoporosis exist (regardless of birth-assigned sex), specifically in those who stop sex hormone therapy after gonadectomy[22].

Gender-affirming surgery

Some transgender subjects request surgery to alleviate the distress caused by the gender incongruence. The type of surgery includes interventions that directly impact fertility and those that do not. Those that affect fertility (previously called sex reassignment surgery, SRS) include genital surgery to remove the gonads, as well as the penis or uterus (in transwomen and transmen, respectively). In Italy, gender-affirming surgery is covered by the NHS. Gender-affirming surgery is often governed by the legal system of the state or country in which it is performed. In Italy, in compliance with Law no. 164/82, which regulates legal gender recognition, access to gender-affirming surgery must be authorized by a court. More recently (July 2015), a decision of the Supreme Court of Cassation (ruling act no. 15138/15) established that surgical sterilization should not be considered strictly necessary for having one's gender identity legally recognized. Subsequently, this decision was supported by the Constitutional Court (ruling no. 221 of 2015).

The description of the surgical techniques is not within the scope of this review. In short, for transwomen surgical options include: orchidectomy, penectomy, vaginoplasty, vulvoplasty, clitoroplasty, breast implants and facial feminization surgery[14,22]. For transgender men surgery may involve: bilateral mastectomy, hysterectomy, salpingo-oophorectomy, phalloplasty or metoidioplasty, scrotoplasty, and testicular and penile implants[14,22]. An endocrinologist or experienced medical provider should monitor transgender individuals after surgery. Those who undergo gonadectomy require hormone replacement therapy, surveillance, or both to prevent the adverse effects of chronic hormone deficiency. Due to the lack of controlled studies, incomplete follow-up, and absence of effective assessment measurements, estimating various surgical approaches and techniques is difficult. However, recent evidence suggests that compli-

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cation rates are high in gender-affirming genital surgery. For instance, for vaginoplasty, Dreher PC et al.[50] report a complication rate of 32.5%, and a re-operation rate, for non-esthetic reasons, of 21.7%. For phalloplasty, Remington AC et al.[51] report a 39.4% rate of urethral complications, the most common kind of complication for this surgery.

Conclusions

Studies carried out across a variety of different contexts have shown that transgender people are a medically-underserved population in both primary and specialist care settings. Despite the growing interest of the scientific community in transgender health, this subject remains understudied. Lack of standardized terminology to describe transgender identity and history, the absence of large prospective observational studies and intervention trials, limited data on the risks and benefits of gender-affirming hormone treatment and surgical interventions are among the main problems to be solved in terms of transgender health research. In addition, given the probable size of the transgender population and the range of healthcare needs, it is crucial that healthcare providers be trained in transgender healthcare (in this regard some initiatives such as master's degrees and online CME course are under way in Italy[52,53]). It is urgently necessary to fill all these gaps to provide effective and appropriate evidence-based prevention and care, in order to assure health equality for transgender people. To this end, close cooperation between public health researchers, policymakers, healthcare providers, communities and their political organizations is essential.

Key messages

- Few data exist on transgender prevalence and this lack of insight poses a problem for healthcare planners. The literature highlights the importance of following standardized definitions, because the results may vary by several orders of magnitude.
- Transgender people often avoid primary care, partly because healthcare providers lack skills in the area of transgender health. Consequently, transgender people often make use of parallel providers and engage in self-administered (and unmonitored) hormone treatment.
- Transgender people share many of the health needs of the general population, but may have special health needs, such as those related to gender-affirming hormone treatment and gender-affirming surgical intervention. Primary care and health maintenance issues should be addressed before, during, and after any changes in gender role and medical interventions to alleviate gender dysphoria.
- Of the possible adverse outcomes of gender-affirming hormone treatment in the transgender population, cardiovascular disease is a specific area of concern. In particular, transgender women treated with estrogens should be monitored for possible deep vein thrombosis.
- Large prospective observational studies and intervention trials on the risks and benefits of gender affirmation treatments (e.g. hormones and surgical interventions) are urgently required.

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